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Gene Section

Mini Review

POLE (DNA polymerase epsilon, catalytic subunit)

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Abstract

Review on POLE, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords

POLE; DNA repair; DNA replication; DNA replicase

Identity

Other names: POLE1

HGNC (Hugo): POLE

Location: 12q24.33

Local order: 132,623,762-132,687,359

DNA/RNA

Description

POLE gene is 63.6 kb long and composed of 49 coding exons, where the first and last one also have a UTR region.

Transcription

The length of the transcript is 7840 bp and results in a protein of 2286 residues.

Protein

Description

The POLE gene encodes for one of the four subunits that form Polε (DNA polymerase epsilon) together with POLE2, POLE3 and POLE4 genes. This protein is one of the main DNA replicases in

eukaryotes and is responsible of the replication of the leading strand. POLE contains both the catalytic active site and the proofreading exonuclease domain (residues 223-517). Accordingly, the POLE gene confers to Pole both replicative and 3' to 5' repair capabilities for the new strand.

Expression

Broadly expressed.

Localisation

Nuclear.

Function

Pole is responsible of the polymerization of the leading strand during DNA replication in yeast and humans. It also possesses 3' to 5' exonuclease capability to repair missincorporated nucleotides during DNA replication. Pole is also involved in DNA repair pathways such as mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER) or double-strand break repair.

Mutations

Germinal

A few missense germline mutations in the proofreading domain of POLE have been shown to be pathogenic such as W347C, N363K, D368V, L424V, P436S or Y458F. These are quite rare in the population although for unclear reasons they are more common than similar germline mutations in the polymerase gene POLD1. These mutations affect the exonuclease repair of Pole hence resulting in a mutation rate increase of about 100-fold.

Accordingly, these tumours are usually called ultramutated.

Somatic

Pathogenic somatic mutations in the proofreading domain of POLE have been found in some tumour types at moderate or rare frequencies. Some mutations in the polymerase domain have been suggested to be drivers but further research is required to validate these results.

Implicated in

Different human sporadic cancers

Somatic pathogenic mutations in the proofreading domain of POLE have been found in 8% of endometrial tumours and at lower frequencies in other tumour types such as colorectal, glioblastoma, ovary, prostate, breast or gastric cancer. These mutations seem to confer similar phenotypes regardless of the tumour tissue type. These are missense, heterozygous mutations where no second hit by either mutation or LOH seem to be required, and they are very early events, possibly initiating. Some mutations are hotspots such as P286R, S297F, V411L or S459F but other rarer mutations have also been identified (eg P286H/L, S297Y, F367S, L424V/I, P436R, M444K, A456P). These mutations affect the proofreading of the protein resulting in ultramutation with an overrepresentation of C>A. More specifically, POLE tumours have mutational signature 10 as reported by Alexandrov et al, with extremely prominent TCG>TTG and TCT>TAT substitutions and transcriptional strand bias. As a result, there is an overrepresentation of some specific missense mutations and nonsense mutations. In addition, it may explain why some cancer driver genes in POLE tumours tend to show mutations otherwise relatively uncommon such as R213X in TP53 or R88Q in PIK3CA. POLE tumours are hardly ever concomitant with microsatellite instability, although a few tumours with both phenotypes have been described, and do not seem to show chromosomal instability as their karyotype is nearly diploid.

Disease

Patients with somatic POLE driver mutations are younger on average, although they have a broad range of ages. For colorectal cancer, most mutations are right-sided so they are relatively rare in rectal cancer.

Prognosis

POLE tumours in endometrial cancer, colorectal cancer and glioblastoma show excellent prognosis in early disease. Similar patterns are expected in any other tumour type although it is not formally proven due to the low frequency of these mutations. Such good prognosis is because of very high

immunogenicity with upregulation of immune checkpoint and other immunosuppressive genes. Accordingly, POLE proofreading pathogenic mutation is also a promising candidate biomarker for checkpoint blockade immunotherapy. They may also be sensitive to treatment with nucleoside analogs as they increase the mutation burden to a level where tumour cells are not viable.

Proofreading-associated polyposis (PPAP)

Disease

Autosomal dominant disease with high risk for endometrial and/or colorectal adenoma or carcinoma due to germline mutations in POLE or POLD1 genes.

Prognosis

Probably good prognosis in early disease as found with POLE somatic mutations, although not formally proven. Similarly, these patients are likely to respond to checkpoint blockade immunotherapy.

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